DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

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JAN 30 2002

Mr. Robert Dettery
Vice President, Regulatory Affairs
Mutual Pharmaceutical Company
1100 Orthodox Street
Philadelphia, PA 19124

Docket No. 01P-0117/CP1

Dear Mr Dettery:

This letter responds to your petition dated March 6, 2001, asking the Food and Drug Administration (FDA) to reclassify metaxalone tablets (brand name Skelaxin) as a drug product with potential or actual bioequivalence problems and to announce the reclassification in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book). You also ask that FDA make inclusion of an *in vivo* fasting bioequivalence study a condition of approval for an abbreviated new drug application (ANDA) for metaxalone tablets and that the Agency not approve an ANDA unless it contains an acceptable *in vivo* fasting study. For the reasons described below, your petition is granted.

FDA found metaxalone tablets to be effective and published its findings in a Drug Efficacy Study Implementation (DESI) notice on August 15, 1974 (39 FR 29396). FDA regulations at 21 CFR 320.22(c) state that *in vivo* bioequivalence will be waived for a drug product determined to be effective for at least one indication in a DESI notice unless the Agency has evaluated the drug product under the criteria set forth in 21 CFR 320.32[1] and rated the drug as having a known or potential bioequivalence problem. FDA did not originally classify metaxalone tablets as having a known or potential bioequivalence problem, and therefore bioequivalence studies have not been required as a condition of approval for ANDAs.

You developed two formulations of metaxalone tablets and performed dissolution testing and *in vivo* fasting bioequivalence studies on both. On the basis of your experience with dissolution and bioequivalence testing of your formulations, you assert that *in vitro* dissolution does not predict *in vivo* performance, and therefore metaxalone tablets should be classified as a drug with an actual or potential bioequivalence problem. For example, your second formulation was not bioequivalent to Skelaxin although it had a dissolution profile that was almost superimposable on Skelaxin's.

[1] Section 320.22(c) mistakenly refers to section 320.32. In fact, the section titled "Criteria and evidence to assess actual or potential bioequivalence problems" is section 320.33. FDA proposed to correct this error in a proposed rule published on November 19, 1998 (63 FR 64222).

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FDA has evaluated the dissolution testing results you submitted with your petition and concurs that the low solubility and slow dissolution rate of metaxalone tablets indicate that metaxalone tablets belong to the category of products with actual or potential bioequivalence problems. The Agency agrees that the *in vivo* bioequivalence data you submitted demonstrates a lack of correlation between *in vitro* dissolution and *in vivo* bioequivalence. Accordingly, your petition is granted. FDA announced its proposal to reclassify metaxalone tablets as a drug product with potential or actual bioequivalence problems in the June 2001 cumulative supplement to the Orange Book. No comments were received, and FDA has reclassified metaxalone tablets as a drug product with potential or actual bioequivalence problems. The Agency will not approve an ANDA for metaxalone tablets unless the results of an *in vivo* fasting bioequivalence study are acceptable.

Sincerely yours,

for Janet W Woodcock
Director
Center for Drug Evaluation and Research